STANDARDISATION and TRACEABILITY in LABORATORY MEDICINE

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LABORATORY MEDICINE

... an integrated discipline in health care:
risk assessment
diagnosis of health and disease,
follow-up and monitoring of patients.

... using physical, chemical, biochemical, immunological, molecular biological techniques for measurements of
body fluids, tissues, and cells

ANALYTES - MEASURANDS

CATEGORY I
Traceable to the SI
Reference Systems

- **creatinine**
- **cholesterol**
  total/fractions
- **enzymes**
- **electrolytes**
  total/activity/free
- **glucose**
- **steroids & thyroxine**
  free/bound to proteins

CATEGORY II
Not-traceable to the SI
Conventional RMs
(international agreement)

- **coagulation factors**
- **glycoproteins**
  isoforms/glycoforms
- **proteins**
  peptide-bond (biuret reaction)
  epitopes (antibodies)

BIOLOGICAL VARIATIONS

Matrix - Fluids

Serum - Plasma
Urine
Liquor
Ascites
Tissue
Cells

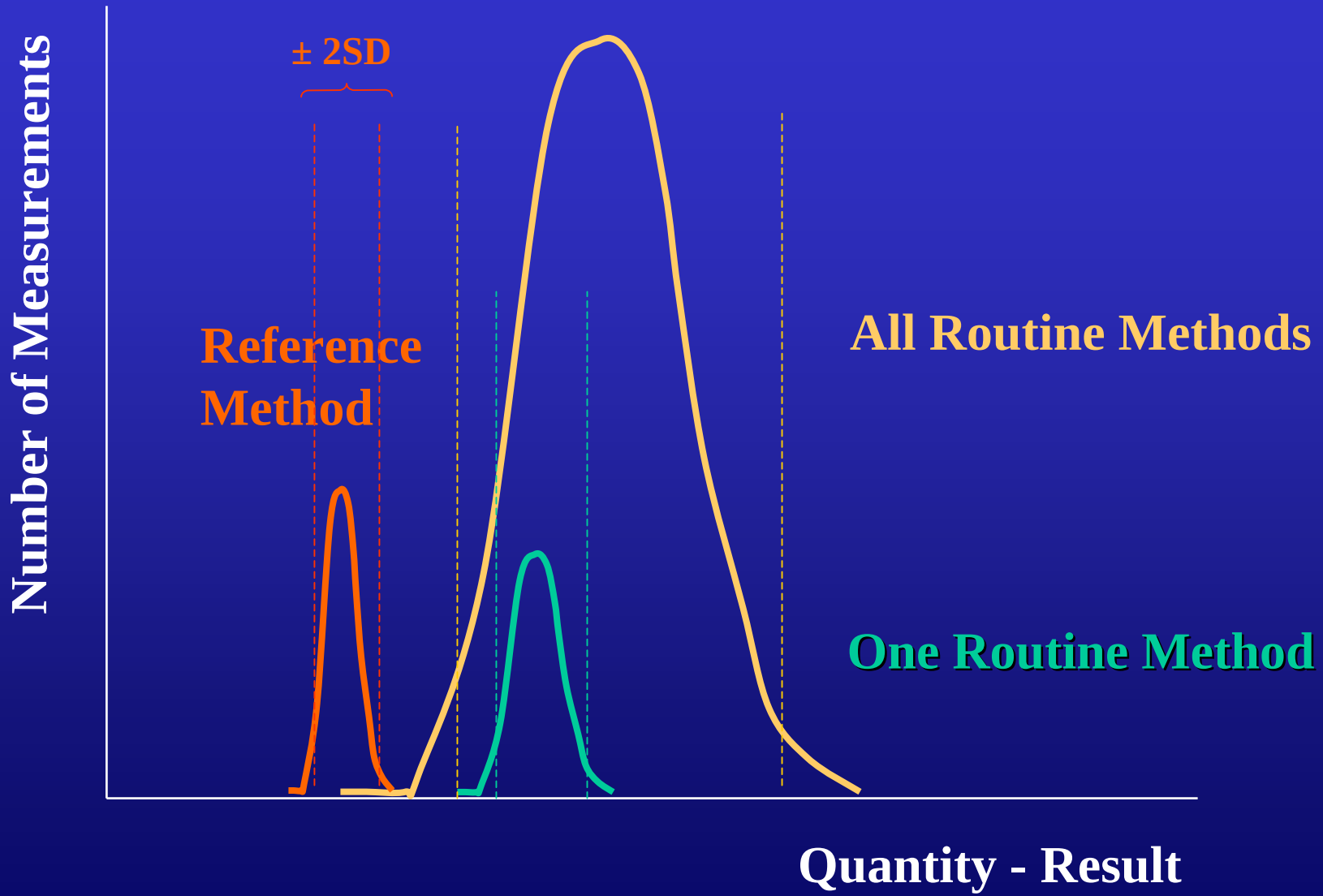
Factors

Age
sex
time of day (circadian rhythm)
posture (supine/upright)
serum/plasma
fasting/non-fasting
weight/overweight
seasonal influence

Intra-individual variations

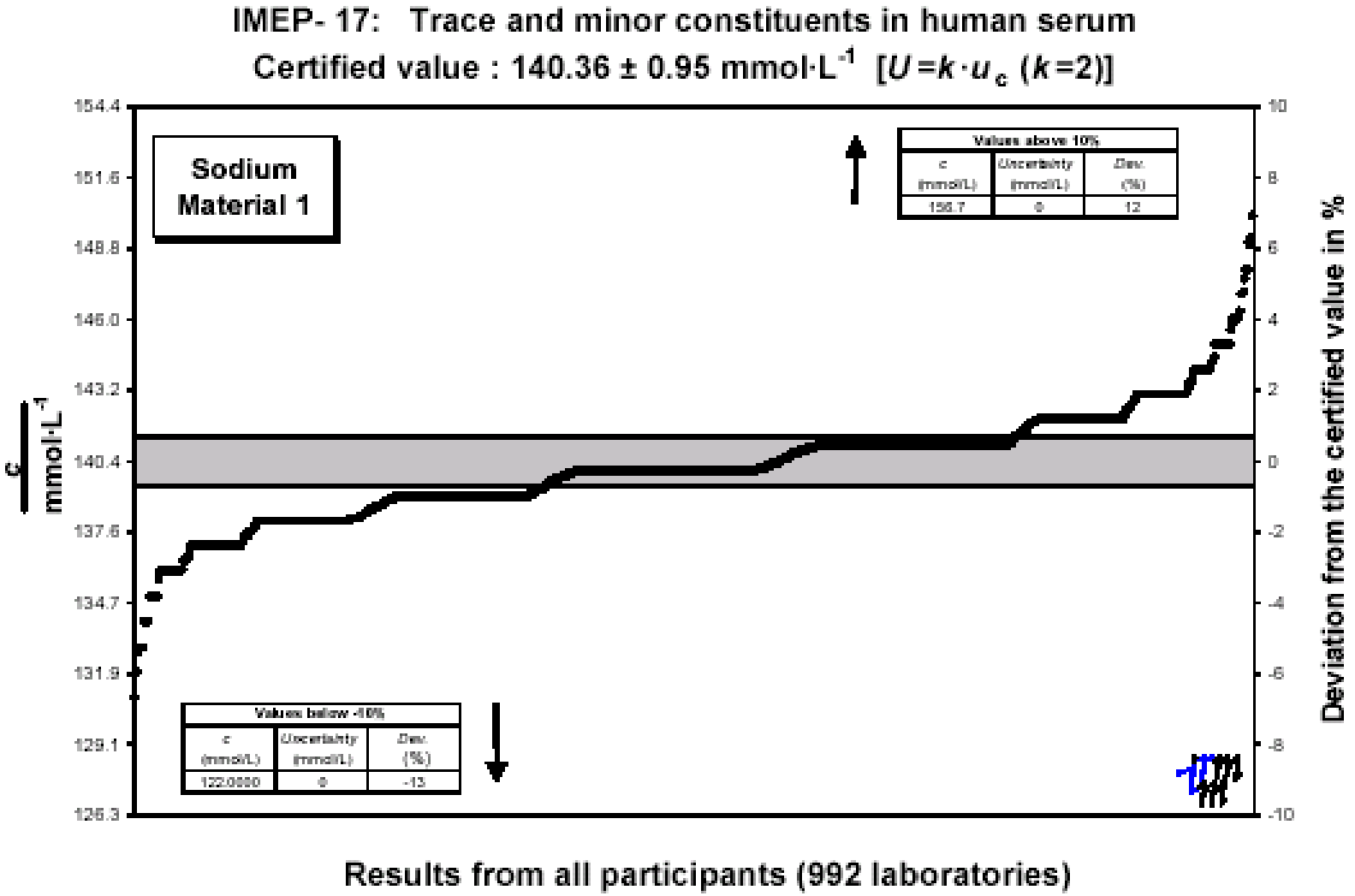
	Analytical CV	Daily %	Weekly %	Monthly %
Na	**0.6**	**1.4**	**0.8**	**1.3**
K	**1.0**	**7.8**	**6.7**	**7.3**
Glucose	**1.5**	**25.8**	**16.8**	**20.8**
Creatinine	**1.6**	**6.8**	**6.9**	**13.6**
Uric acid	**1.0**	**9.8**	**12.4**	**14.3**
ALT (enzyme)	**0.9**	**10.3**	**32.2**	**47.5**

ANALYTICAL BIAS

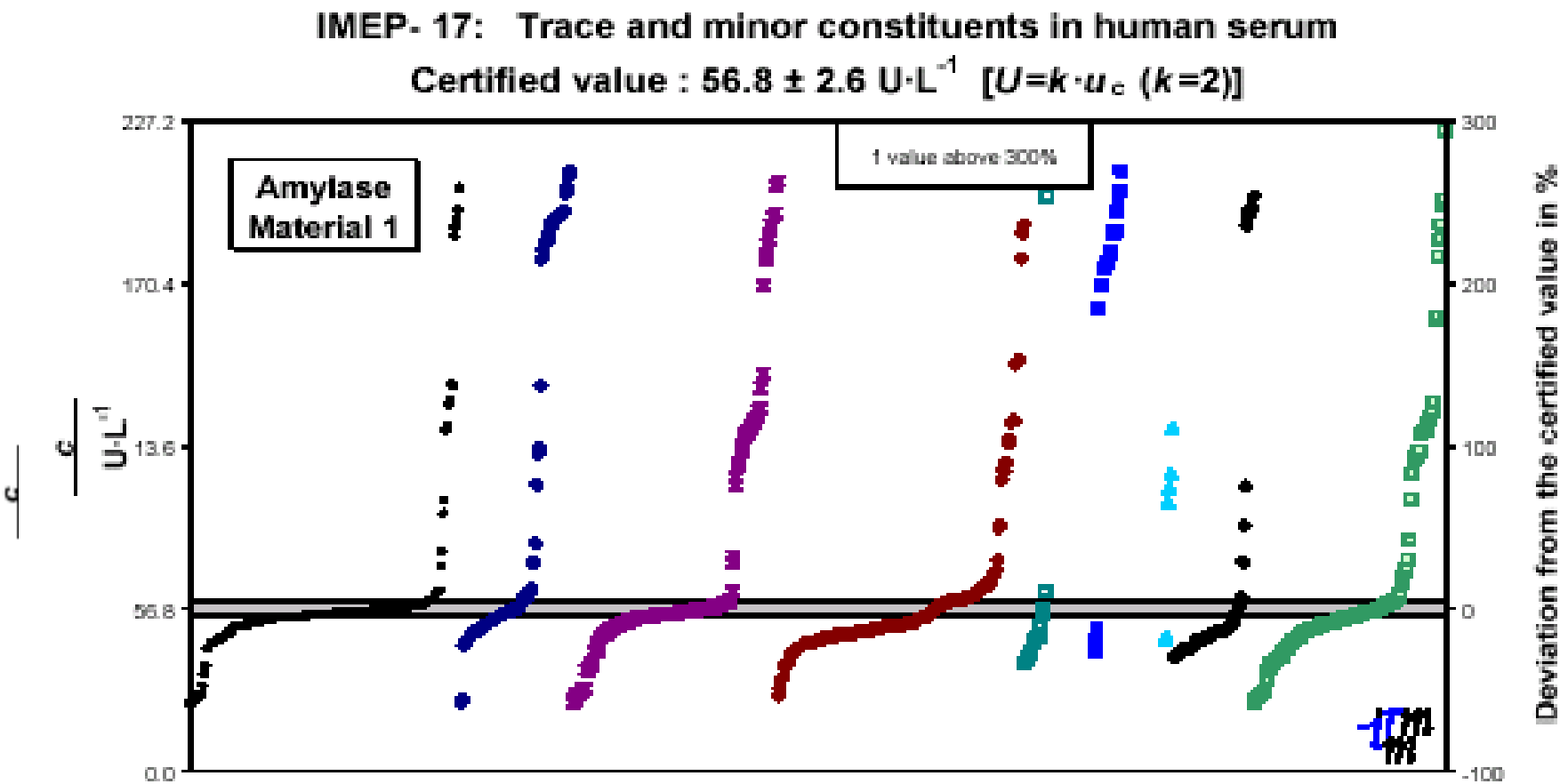


R. DYBKAER 1975

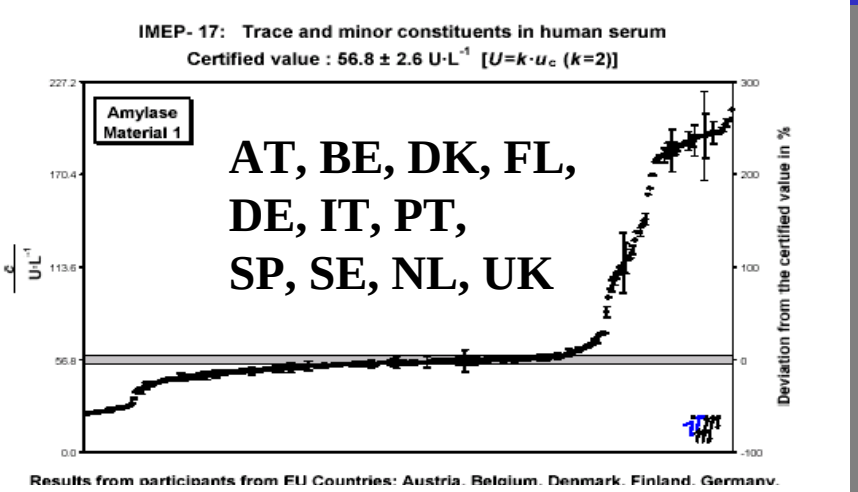
International Comparison

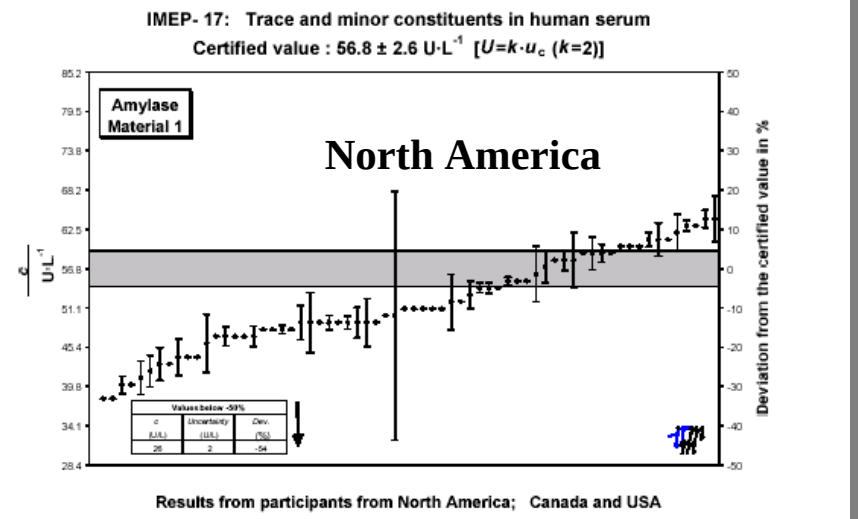


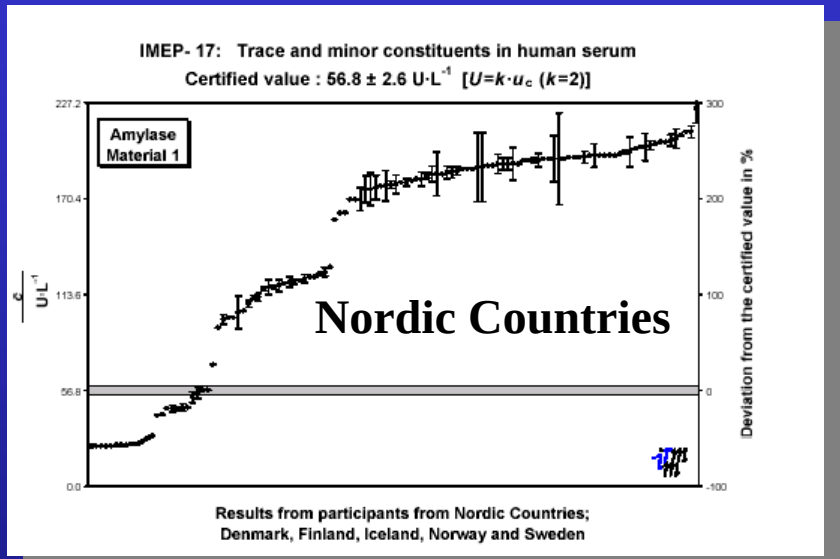
Amylase Comparison



Amylase Comparison







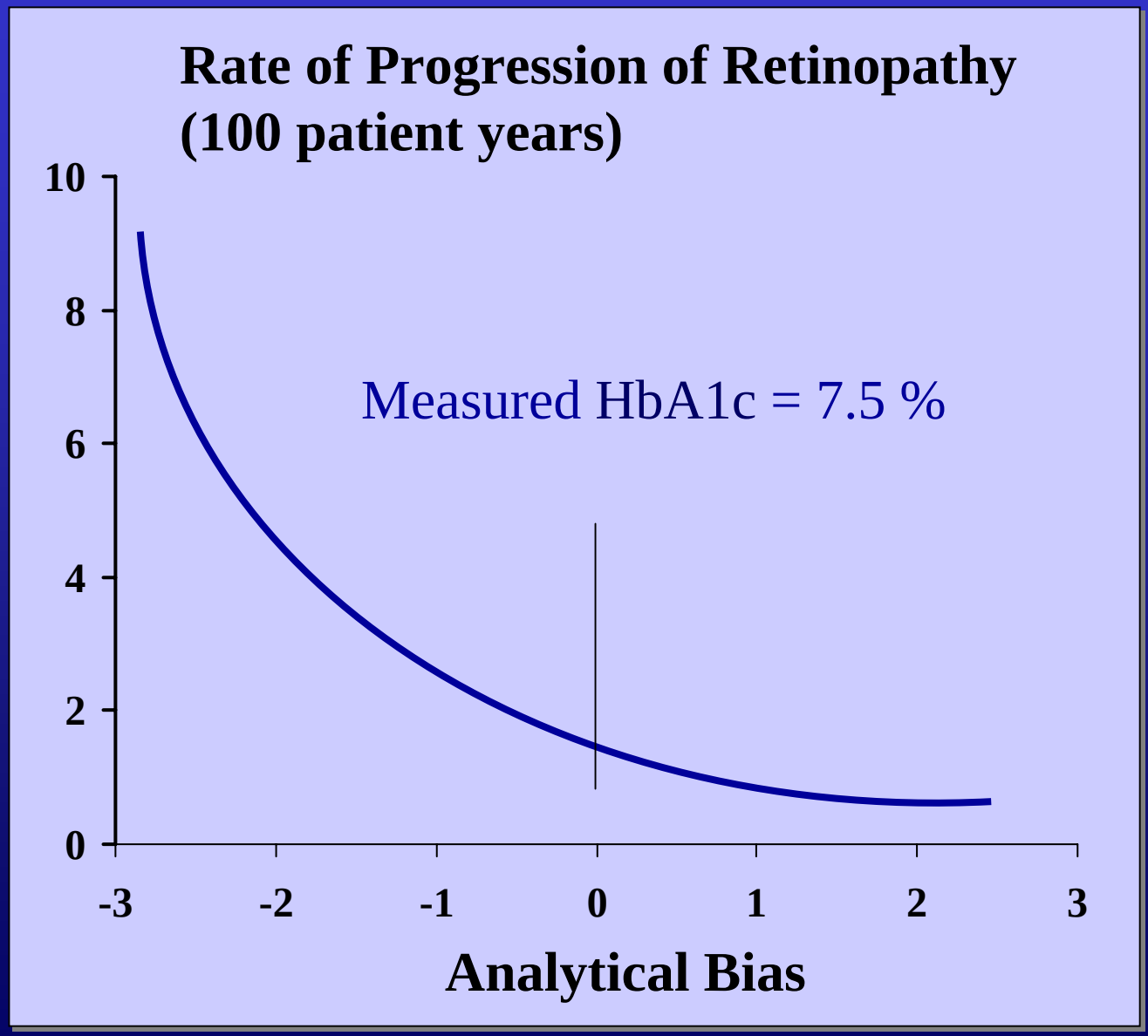
- Difference in field methods
- Patient results not comparable

Need for Harmonisation

Analytical Bias - Therapeutic Consequence

HbA1c

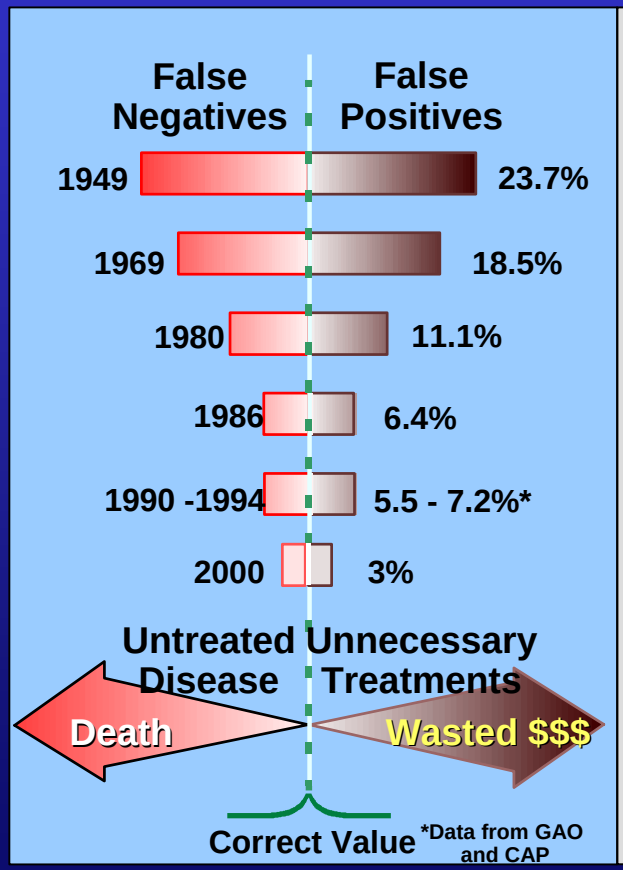
Insulin-dependent patients



P. Hyltoft Petersen et al 1997

Cholesterol Measurements

Improved Cholesterol Measurement Accuracy Saves Health Care Dollars



NIST Contributions to National Reference System for Cholesterol

1967 – Pure Cholesterol SRM *(SRM 911)*

1980 – Cholesterol in Serum Definitive Method

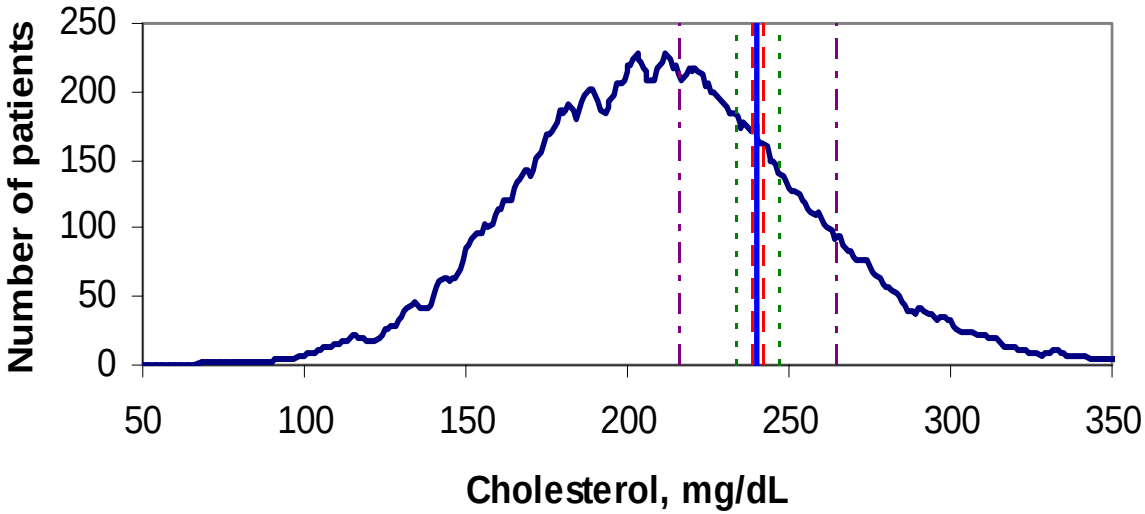
1981 – First Cholesterol in Human Serum SRM *(SRM 09)*

1988 – New Suite of Cholesterol in Serum SRMs at MedicalDecision Points

1997 – New Suite of Fresh-Frozen Serum SRMs designed to address clinical analyzer commutability issues; Total-, HDL-, and LDL-Cholesterol and Triglyceride Values

Improvement in precision since 1968 has been estimated to save $100M/yr in treatment costs

Bias in Cholesterol Measurement Effects Medical Decision-Making



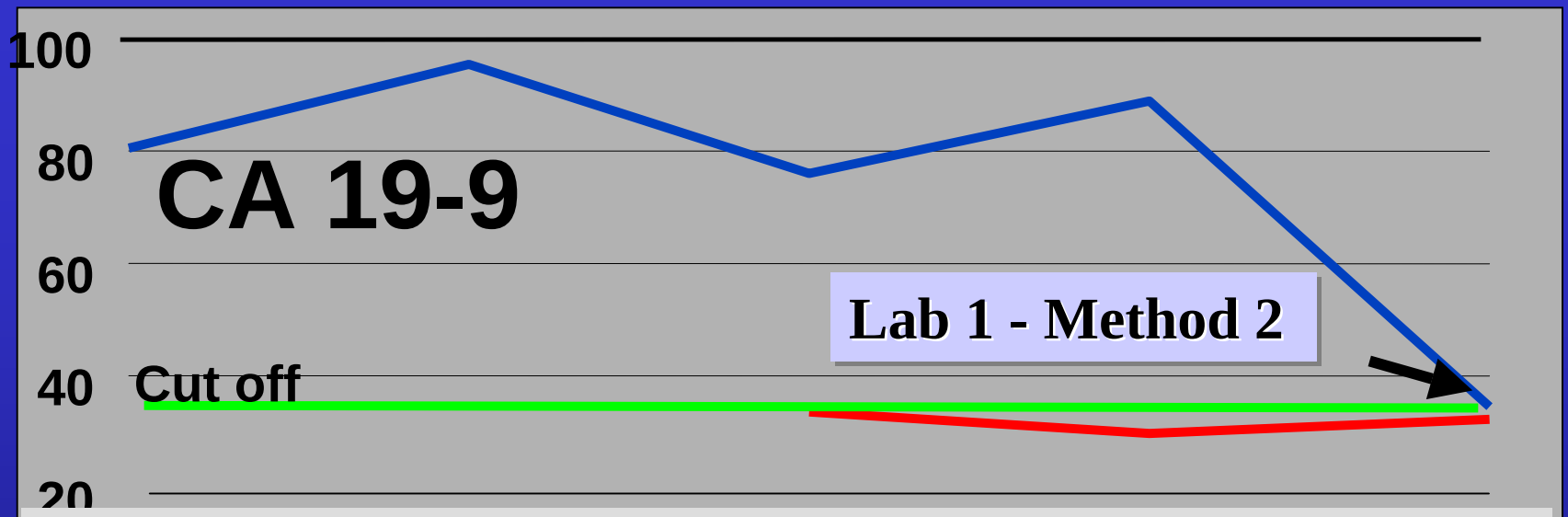
Cholesterol Frequency Distribution of >20,000 Mayo Clinic Patients
(with +1%, +3% and +10% limits around 240 mg/dL criteria point)

If measurement bias were:	Positives (>240 mg/dL) per 1000	Predicted Change in "Positives/1000"
-10% bias	120	-129
-3% bias	203	-46
-1% bias	234	-15
0% bias	249	
+1% bias	263	+14
+3% bias	300	+51
+10% bias	446	+197

AQAS - Method Target Values in 2 Control Samples

Analyte	LIA	EIA	MEIA	RIA
AFP (ng/ml)	39 79	32 93	35 99	26 72
CEA (ng/ml)	4 28	5 31	4 25	4 28
CA 19-9 (U/ml)	12 63	21 84	26 87	15 52
PSA (ng/ml)	12 120	7 70	7 80	

Performance of 2 Field Methods



Diagnostic procedures	Costs - €
CA 19-9 tests	246
X-Ray	157
Ultrasound	1062
Computer tomography	1062
NMR	1194
	2,871

Consequences for the Patient

EQUAS Results
Clinical Guidelines for Decisions

NEED FOR INTERNATIONAL STANDARDISATION

- Characterisation of Analyte
- Clinical Needs
- Reference Procedure
- Reference Material
- Reference Laboratories

STANDARDISATION

A technical process to reach conformity of measurement procedures by applying highest scientific standards

REFERENCE SYSTEM

REFERENCE METHODS
REFERENCE MATERIALS
REFERENCE LABORATORIES

- **ISO/EN 15195**

  Requirements for **reference measurement laboratories** in laboratory medicine

- **EN 12286**

  Measurements of quantities in samples of biological origins – Presentation of **reference measurement procedures**

- **EN 12287**

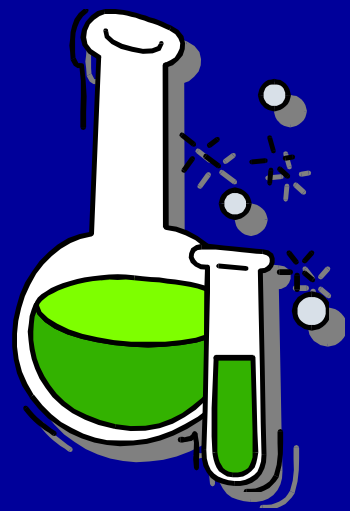
  Description of **reference materials**

- **FULL NATIONAL MEMBER SOCIETIES: 79**
- **AFFILIATE MEMBER SOCIETIES: 4**
- **CORPORATE MEMBERS: 38**

- **REGIONAL ORAGNISATIONS AFFILIATED WITH IFCC**
  - **Arabic Federation of Clinical Biology**
  - **Asian Pacific Federation of Clinical Biochemistry**
  - **Colabiocli - Latin American Federation**
  - **FESCC - Federation of European Societies**

ifcc SCIENTIFIC DIVISION
REFERENCE METHODS

- **ENZYMES**
  - ALAT, ASAT, Amylase, AP, CK, gGT, LDH
  - Lipase (in preparation)
- **BLOOD GASES - ELECTROLYTES**
  - Tonometry
  - pCO_2
  - Na, K, $Ca_{ionised}$
- **PROTEINS**
  - Apo A1
  - Hb
  - HbA1c



AQAS Interlaboratory Comparison

Source: Austrian Clinical Chemistry Surveys

ANALYTE	1970	1982	1992	2001	2003
Participants	36	269	603	1358	1812
AP	33.9	11.5	5.6	5.9	5.1
ALAT	67.8	17.2	5.0	5.9	5.7
ASAT	36.3	20.8	5.3	6.0	5.8
LDH	32.0	10.1	5.9	3.7	4.0

CV %

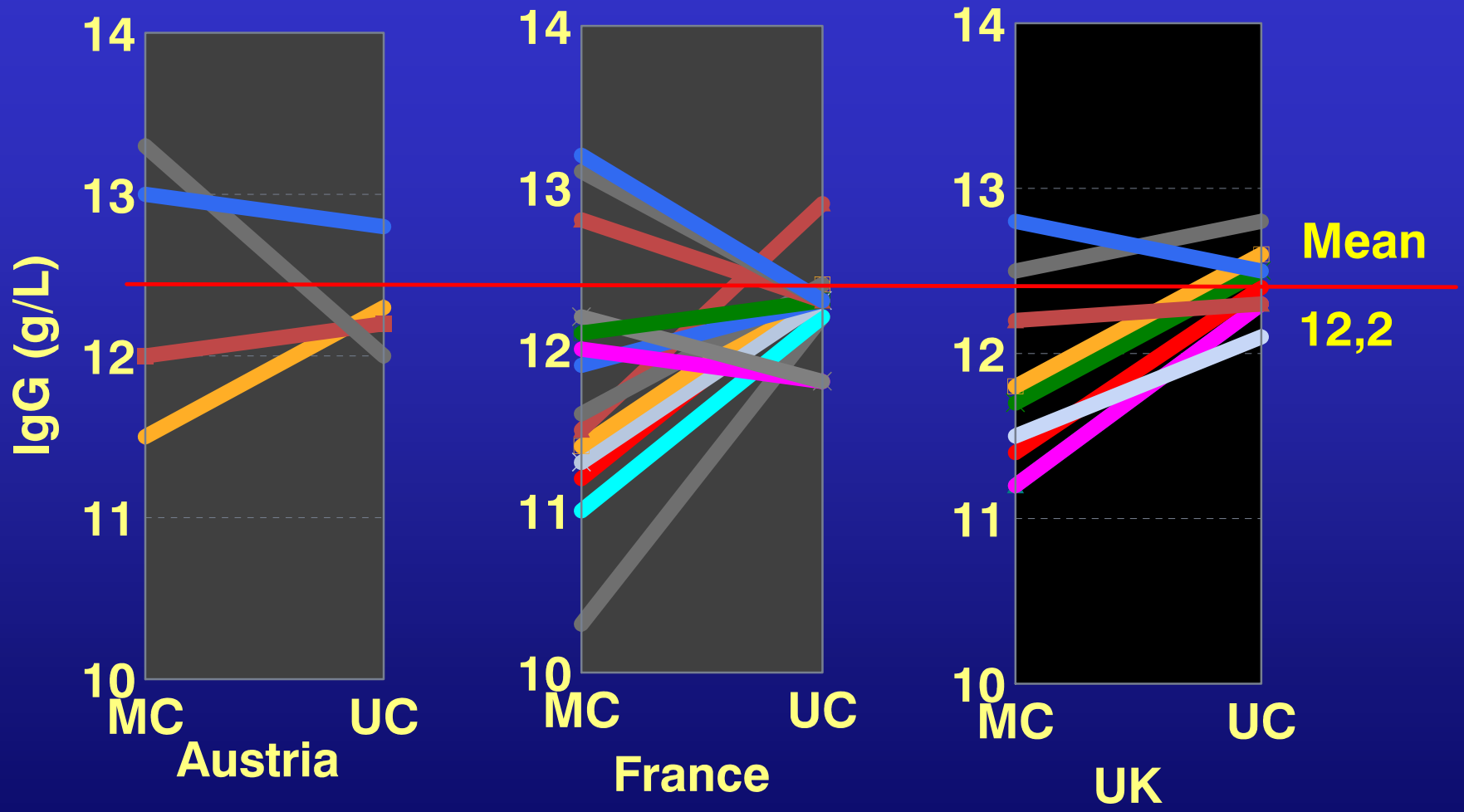
SCIENTIFIC DIVISION

ifcc

REFERENCE MATERIALS

Apo A1	WHO: SP1
Apo B	WHO: SP 3
Albumin	WHO: 74/1
Plasma Proteins	IRMM: CRM 470
PSA, free, complexed	WHO: 96/668, 96/670
ALAT	IRMM: 454
Amylase	IRMM: 456
CK-MB	IRMM: 455
gGT	IRMM: 452
LDH-1	IRMM: 453
Cortisol	IRMM: 451
HCG primary standards	WHO: 99/642, 650, 688, 692, 708, 720,
Lp(a)	WHO: 03/
ASAT, HbA1c, myoglobin	IRMM: in preparation

CRM 470's EFFECT ON CALIBRATION



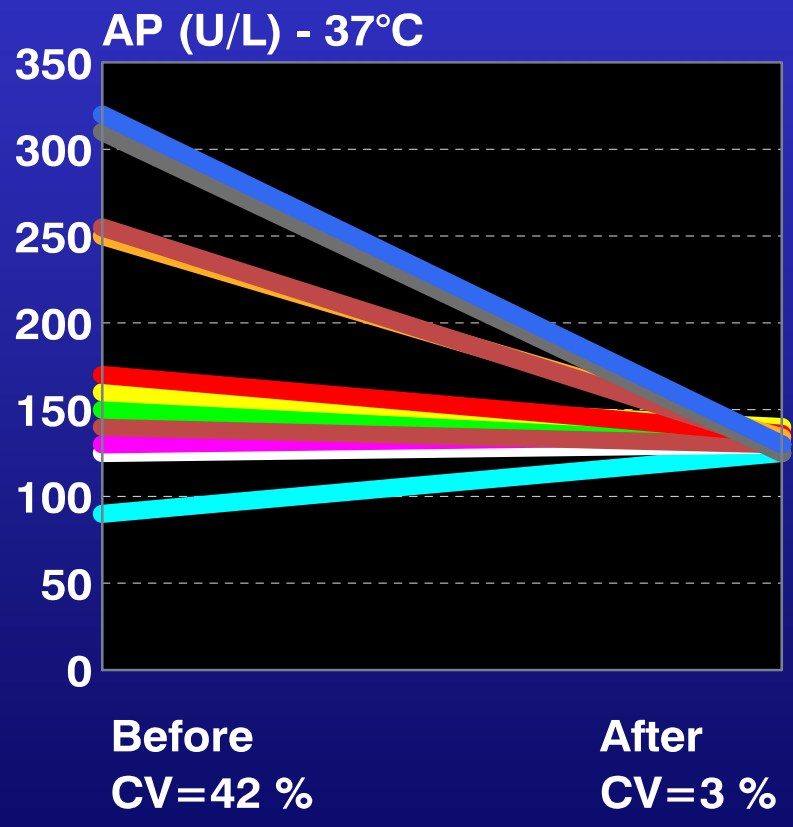
MC = different Calibrators UC = CRM 470

Bullock D. G. 1990

ifcc SD

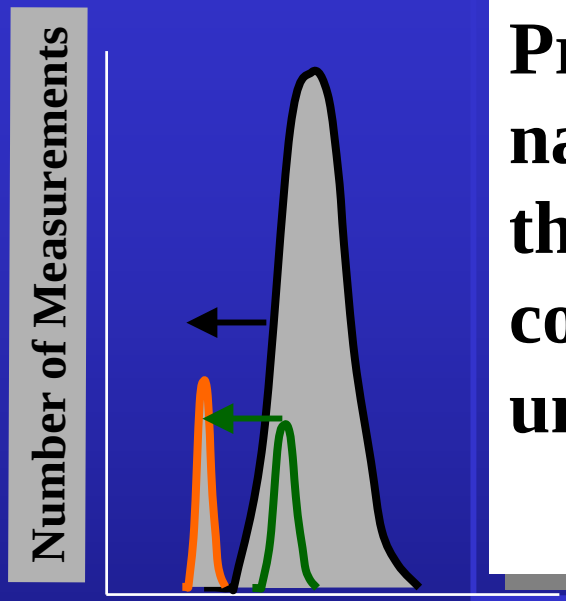
WG-CALIBRATORS IN CLINICAL ENZYMOLOGY (WG-CCE)

Effect of Uniform Calibration on Various Methods



G. FERARD, J. M. LESSINGER 1998

TRACEABILITY



Property of the result related to national or international standards through an unbroken chain of comparisons all having stated uncertainties.

A: traceable to SI
B: non-traceable to SI

- **Int'l Rreference measurement procedure and int'l calibrator**
- **Int'l Reference measurement procedure but no int'l calibrator**
- **Int'l calibrator but no int'l reference measurement procedure**
- **Manufacturer's measurement procedure but neither int'l reference measurement procedure nor int'l calibrator**

IVD-Directive 98/79

The **traceability** of values assigned to calibrators and or control materials must be assured through **reference measurement procedures and reference materials** of a higher order

ISO Standards

In vitro diagnostic medical devices - Measurements of quantities in biological samples

- **ISO 17511**– **Metrological traceability** assigned to calibrators and control materials.
- **ISO 18153** – **Metrological traceability** of values for catalytic concentration of enzymes assigned to calibrators and control materials.

JOINT COMMITTEE on TRACEABILITY in LABORATORY MEDICINE

JCTLM
a global initiative,
formed
in Paris, June 12, 2002

http://www.bipm.org/enus/2_Committees/JCTLM.shtml

JCTLM
Joint Committee for Traceability in Laboratory Medicine

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- …e d… o…
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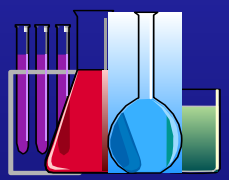
  …requirements


Establishment of
a global

REFERENCE SYSTEM,

TRACEABILITY



needs collaboration and mutual recognition between Professionals, Metrology Institutes, Regulators, and IVD-Industry

A JOINT VENTURE OF PROFESSIONALS

Focus on Standardisation and Traceability

- Excellence in Analytical Performance based on modern concepts of metrology and science
- Needs for Patients
- Impact on Clinical Decisions

...will add QUALITY and VALUE to
CLINICAL CHEMISTRY
and
LABORATORY MEDICINE